32. (Amended) A method of prophylaxis, diagnosis and treatment, comprising:

assessing cell activation; and, if elevated,

administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of treatment of a disease or disorder.

REMARKS

A check for the fee for a one month extension of time accompanies this response. Any fees that may be due in connection with filing this paper or with this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 10-18, 32-36, 38, 41 and 42 are presently pending in this application. Claim 10 is amended by incorporating the preamble into the body of the claim. No new matter has been added.

THE REJECTION OF CLAIMS 10-18, 32-36, 38, 41 and 42 UNDER 35 U.S.C. §103

Claims 10-18, 32-36, 38, 41 and 42 are rejected under 35 U.S.C. 103 as being unpatentable over Okada *et al.* ((1991) *Journal of International Medical Research 19*:234-236) (Okada 1), Okada *et al.* ((1991) *Journal of International Medical Research 19*:348-350) (Okada 2), Yanamoto *et al.* or Yonekura *et al.* in view of Gibboni *et al.*, Babcock *et al.*, and Brunck *et al* because applicant is allegedly claiming a method of treating or preventing disorders using a protease inhibitor, and Okada 1, Okada 2, Yanamoto, and Yonekura allegedly teach administering futhan, to a patient. Gibboni and Pick each is alleged to teach that assays using phenol red are well known to be used for the measurement of hydrogen peroxide produced by cells in culture and, thus, the measurement of free radical production. Gibboni also is alleged to teach that such assays are useful for patients to check their cholesterol or glucose levels. Babcock is alleged to teach that traumas can be treated by administering compounds that

scavenge free radicals. Brunck is alleged to teach that trauma, such as pancreatitis, is known to be treated by futhan.

Without citing any references, the Examiner states that since such patients would normally check their glucose levels, they would be motivated to treat their glucose overproduction if the levels were too high. Similarly, the Examiner reasons that someone who had a trauma would want to know before that condition was treated (if it needed to be treated) by futhan whether or not free radical production had occurred. The Examiner is of the opinion that it would have been within the purview of the skilled artisan to administer the phenol red assay first to detect the free radical production and, if elevated, the measurement would indicate that treatment for the trauma would need to be performed. Such treatment would be the administration of futhan.

In addition, again without citing any art, the Examiner reasons that, if someone has a trauma, such as pancreatitis, which is known to be treated by administering futhan, it would have been well within the purview of the "skilled artisan" to treat a trauma with futhan and to assess the treatment to see if it was necessary by using the phenol red assay since it is well known that phenol red assays are used to detect free radical production and that traumas are treated by compounds such as futhan and further that traumas are treated by compounds that scavenge free radicals.

The Examiner further reasons that since traumas are treated with futhan and traumas produce free radicals, it would have been obvious to use a compound like futhan after the detection of elevated free radical production by phenol red assay, to treat the patient in an effort to reduce the free radical production.

This rejection is respectfully traversed.

The Office Action has failed to set forth a case of *prima facie* obviousness

Relevant law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 U.S.P.Q. 471 (Bd. App. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" (*In re Keller*, 642 F.2d 413, 425, 208 U.S.P.Q. 871, 881 (CCPA 1981)), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983). Importantly, **all claim limitations** must be taught or suggested by the prior art to establish that claims are *prima facie* obvious. *See, e.g.,* MPEP 2143.03 and *In re Lowry*, 32 F.3d 1579, 32 U.S.P.Q.2d 1031 (Fed. Cir. 1994), citing *In re Gulack*, 703 F.2d 1381, 217 U.S.P.Q. 401 (Fed. Cir. 1983), citing *In re Royka*, 490 F.2d 981, 180 U.S.P.Q.2d 580 (CCPA 1974).

Analysis

The Claims

Claim 10 is directed to a method of improving treatment outcome or reducing risk of treatment by assessing treatment options by:

1) measuring cell activation levels in a subject;

2) if elevated cell activation levels are elevated, administering activation lowering therapy **prior** to commencing any treatment for the disease or condition. The cell activation therapy, such as administration of futhan, is **not** the treatment for a disease or condition, but refers to testing and therapy to be administered **before treating a disease or condition.**

Claim 32 is directed to a method of prophylaxis, diagnosis and treatment, by assessing cell activation; and, if elevated, administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of treatment of a disease or disorder.

As described in the application on page 16, lines 19-25, cell activation refers to changes in and interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets. These changes are evidenced by increased "stickiness" of cells, changes in shapes of cells, free radical production and release of inflammatory mediators and enzymes. Activated cells project large pseudopods, and express adhesion molecules on their surfaces.

The methods of the claims, assess the levels cell activation by measuring indicators thereof. If the levels are elevated, then treatment, to lower cell activation, is initiated to lower it. The steps of these methods are either prior to treatment for a particular disease (claim 10), or are either prophylactic where there is no evidence disease or as way to improve the risks of treatment.

Differences between the claims and the teachings of the cited refer nc s

Okada 1 and 2

The Okada references teach that complement activation is involved in insulin-dependent diabetes mellitus and that futhan is an inhibitor of complement activation. Okada 1 teaches that futhan lowers cytotoxicity activity of sera as measured by chromium release assay. Okada 1 does not teach the not does teach assessing cell activation. nor administration of futhan to lower cell activation, nor does Okada 1 teach or suggest a method in which cell activation is assessed and, if elevated treated, as way of preventing disease or as a way of reducing the risk of a poor outcome of a treatment.

Okada 2 presents a study of the effect of futhan on complement activation in an adult male with insulin-dependent diabetes mellitus and provides evidence of complement activation in insulin-dependent diabetes mellitus. Okada 2 does not teach assessing cell activation nor teach or suggest administration of futhan to lower cell activation, and nor does Okada 2 teach or suggest a method in which cell activation is assessed and, if elevated treated, as way of preventing disease or as a way of reducing the risk of a poor outcome of a treatment.

Yanamoto *et al.*

Yanamoto *et al.* reports the therapeutic effect of futhan for treating cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Yanamoto *et al.* does not teach any cell activation lowering treatment, nor a method in which cell activation levels are assessed, and, if elevated cell activation lowering therapy is a administered, either for prophylaxis (claim 32) or prior to administering treatment for a disease or condition. The reference only teaches that futhan can be used to treat cerebral vasospasm.

Yonekura *et al.*

Yonekura *et al.* teaches the effects of treatment of disseminated intravascular coagulation (DIC) with nafamostat mesylate (futhan). Yonekura *et al.* teaches that futhan inhibits proteinases of the coagulation, fibrinolysis, Kallkrein kinin and complement systems. Yonekura *et al.* does not teach or suggest a method is which cell activation levels are measured, and if elevated, administering cell activation lowering therapy; nor does it teach or suggest a method of prophylaxis or reduction of the risk of poor outcome of treaments. Yonekura does not teach that futhan lowers cell activation. The reference only teaches that futhan may be used to treat disseminated intravascular coagulation.

Gibboni *et al.* and Pick *et al.*

Each of Gibboni *et al.* and Pick *et al.* teaches the use of phenol red assays for the measurement of hydrogen peroxide. Pick *et al.* teaches a method for assessment of hydrogen peroxide produced by cells in culture. It does not teach or suggest a method for measuring cell activation.

Gibboni *et al.* teaches dyes for use in detecting hydrogen peroxide in a sample. Gibboni *et al.* does not teach or suggest measurement of cell activation.

Thus, neither Gibboni nor Pick teaches or suggest that measurement of hydrogen peroxide can be used as a measure of cell activation as a therapeutic indicator. The references do not discuss treatment of any kind and, thus, do not teach or even suggest that an assay for the measurement of free radicals could be used in a method for improving treatment outcome or reducing risks of treatment (claim 32) nor a method of measuring cell activation levels and then, if elevated, administering cell activation therapy prior to treatment of the disease or disorder (claim 10).

Babcock *et al.*

Babcock *et al.* teaches the use of aminosteroids for prophylaxis and treatment of ophthalmic diseases or disorders. The compounds are used to treat oxidative intraocular damage by arresting oxidative processes that cause damage to the eye.

Babcock *et al.* does not teach or suggest methods in which cell activation is assessed, and if elevated, administering cell activation-lowering therapy either prior to further treatment for a disease (claim 10) or as prophylactic measure (Claim 32).

Brunck *et al.*

Brunck *et al.* teaches compounds, such as futhan, that have activity against as inhibitors of pancreatic trypsin, and their use in the prevention and treatment of the tissue damage or destruction associated with pancreatitis resulting from digestive enzymes activated by trypsin. Brunck *et al.* only teaches that digestive enzymes activated by trypsin are elevated in pancreatitis.

Brunck *et al.* does not teach or suggest a method in which cell activation levels are assessed, and if elevated, therapy to lower the levels is administered before administering treatment for a disease or disorder or as a prophylactic measure or for reducing risk of poor outcome of treatment (claim 32). As with all of the cited references the steps of assessing cell activation and administering cell activation lowering therapy (as a therapy to reduce cell activation) prior to treatment for a disease or for prophylactic purposes is not taught or suggested.

There was no Motivation to have Combined the teachings of Okada 1, Okada 2, Yanamoto or Yonekura with Gibboni or Pick, Babcock, and Brunck

There is no motivation or suggestion from the references that would have lead to this combination absent the teachings of the instant application. Each of the references teaches a unique method, separate and complete in itself; there is

no teaching in the references related to futhan therapy that links them to the references that teach methods of measuring free radical production.

The Okada references illustrate a method of treating insulin-dependent diabetes mellitus by administering futhan. Yanamoto *et al.* reports the therapeutic effect of futhan for treating cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Yonekura *et al.* teaches the effects of treatment of disseminated intravascular coagulation (DIC) with futhan. There is no motivation to combine any of these methods of using futhan with the methods of Gibboni *et al.*, Pick *et al.*, Babcock *et al.* and/or Brunck *et al.*. Each of Gibboni *et al.* and Pick *et al.* teaches a method for measuring free radical production. There is no motivation or suggestion from the references to measure free radical production prior to delivering futhan. The Okada references, Yanamoto *et al.* and Yonekura *et al.* teach treatments that happen to result in cell activation lowering, but they do not teach that this is the effect of futhan or any other therapy; rather futhan is administered to treat a particular disorder. None measuring cell activation levels, none suggests lowering cell activation if cell activation levels are elevated.

Brunck *et al.* teaches that futhan inhibits trypsin that can be administered as a treatment for pancreatitis in which digestive enzymes cause tissue destruction. As with Okada (1), Okada (2), Yanamoto *et al.* and Yonekura *et al.*, there is no motivation or suggestion in Brunck to measure free radical production prior, nor administration of cell activation lowering therapy. nor is there a suggestion a method of treatment or prophylaxis.

Brunck *et al.* teaches a method of treating a particular disease, not a precursors (high levels of cell activation) to a disease. Babcock teaches the use of aminosteroids for arresting oxidation processes in the eye for preventing or treating ophthalmic diseases or disorders, but does not suggest methods in which cell activation levels are measured prior, and if elevated, cell activation lowering therapy is administered prior to commencing therapy for a disease

(claim 10). Further neither Brunck *et al.* nor Babcock *et al.* teaches a method of prophylaxis or reduction of risk of poor outcome, by first measuring cell activation levels, and, if they are elevated administering cell activation lowering therapy. Brunck *et al.* and Babcock *et al.* as the Okada references Yamomoto *et al.*, and Yonekura *et al.* are directed to methods of treating particular diseases; none teach or suggest methods of treating cell activation as a precursor to treatment for disease or as a prophylactic measure.

Gibboni *et al.* and Pick *et al.* do not teach or suggest the measurement of cell activation as part of a therapeutic protocol, and none suggest such combination. Gibboni *et al.* and Pick *et al.* are each directed to particular assays to measure measurement of hydrogen peroxide.

Thus, there is no motivation from the teachings of the references to have combined the teachings of Okada (1), Okada (2), Yanamoto *et al.* Yonekura *et al.* and/or Brunck *et al.* with those of Gibboni *et al.* and/or Pick *et al.* These references do not teach that futhan can be used to arrest oxidative processes. More importantly, as addressed below, even if there was motivation to combine the cited references, the combination of references does not result in the claimed methods.

The Combination of teachings of Okada 1, Okada 2, Yanamoto or Yonekura with Gibboni or Pick, Babcock, and Brunck Fails to Result in the Claimed Methods

Even if there had been motivation to combine Okada 1, Okada 2, Yanamoto or Yonekura with Gibboni or Pick, and Babcock, and Brunck, the combination fails to teach or suggest all of the elements of the claimed methods. None of the references teaches or suggests a method that includes the steps of assessing cell activation levels, and, if elevated administering cell activation lowering therapy.

Yanamoto teaches treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage with futhan; Yonekura *et al.* teaches the effects of treatment of disseminated intravascular coagulation (DIC) with nafamostat mesylate (futhan); Babcock *et al.* teaches the use of aminosteroids for arresting oxidation processes and prophylaxis and treatment of ophthalmic diseases or disorders; Brunck *et al.* teaches compounds that have activity against trypsin, such as futhan, for the treatment of the tissue damage or destruction associated with pancreatitis.

These references fail to teach or suggest a method of improving treatment outcome or reducing risk of treatment, by assessing treatment options for a disease or condition by measuring cell activation levels in a subject; and, if elevated, administering activation lowering therapy prior to commencing further treatment for the disease or condition, thereby improving treatment outcome or reducing risk of treatment; nor a method of prophylaxis, diagnosis and treatment by assessing cell activation; and, if elevated, administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of treatment of a disease or disorder.

In none of the treatment methods is the step of measuring cell activation levels prior prophylactically or prior to treatment taught or suggested, nor is a step of assessing cell activation levels taught or suggested, nor is a step of administering cell activation lowering therapy prophylactically or prior to administration of treatment for a disease. In all references in which futhan is administered, it is administered as the treatment for a disease, not for cell activation lowering therapy, and certainly not following assessment of cell activation.

Neither Gibboni *et al.* nor Pick *et al.* cure these deficiencies. Each of Gabboni *et al.* and Pick *et al.* teaches an assay for measuring hydrogen peroxide. Neither reference teaches or suggests assessing the levels cell activation. Neither references teaches or suggests administering treatment to

lower cell activation, if cell activation levels are high. The steps of the claimed methods are either prior to treatment for a particular disease (claim 10), or are prophylactic (claim 32) where there is no evidence disease or as way to improve the risks of poor outcome of treatment (claim 32).

Therefore, the combination of teachings of the references does not result in the instantly claimed methods. No combination of teachings of any or all of the cited references teaches or suggests a method (claim 10) of improving treatment outcome or reducing risk of treatment by assessing treatment options by:

1) measuring cell activation levels in a subject; and

2) if cell activation levels are elevated, administering activation lowering therapy **prior** to commencing any treatment for the disease or condition. The cell activation therapy, such as administration of futhan, is **not** the treatment for a disease or condition, but refers to therapy to be administered **before treating a disease or condition.**

No combination of teachings of any or all of the cited references teaches or suggests a method a method of prophylaxis, diagnosis and treatment (claim 32), by assessing cell activation; and, if elevated, administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of treatment of a disease or disorder.

Thus, the combination of teachings of the cite reference does not result in the instantly claimed methods. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

The Combination of References is based on Hindsight

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L.*

Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983).

The teachings of the combination of references do not result in the instantly claimed methods. For the combination of teachings to result in the methods as claimed, requires use of the teachings of the application at issued. To produce the claimed methods, requires picking and choosing portions of methods taught in the cited references, combining them as claimed in the application and adding teachings of the instant application. The claimed subject methods not prima facie obvious because the combination of teachings of the references does not result in the instantly claimed methods.

For example, it is inappropriate for the Examiner to pick the part of the method of Gibboni that relies on the measurement of hydrogen peroxide in cultured cells Although Gibboni illustrates a version of measuring free radical production, the method is not compatible with the instant claims. As described in detail above, Gibboni teaches detection of an analyte by reaction with an enzyme linked to a dye. The reaction produces hydrogen peroxide that reacts with the dye to produce a color change. Furthermore, the references provide no motivation to modify such an assays to assess cell activation. The Examiner has, therefore, relied on what is taught by the instant application.

Furthermore, it is inappropriate for the Examiner to pick the part of the method of Babcock that relies on treating ophthalmic diseases with compounds that scavenge free radicals and the portion of Brunck that relies on treating pancreatitis on futhan to arrive at the conclusion that, "since traumas are treated with futhan and traumas produce free radicals, it would have been obvious to use a compound like futhan after the detection of elevated free radical production, to treat that patient with futhan in an effort to reduce the free radical production." None of the references teaches detecting elevated free radical production, and then, if elevated, administering treatment to reduce it.

Therefore, the Examiner has improperly relied on hindsight in setting forth the rejection, and has failed to set forth a *prima facie* case of obviousness.

Rebuttal to the Examiner's Arguments

The Examiner cannot take official notice of facts outside the record that are not capable of instant and unquestionable demonstration. The Examiner makes quite a few such allegations.

Without citing any references, the Examiner states that since such patients would normally check their glucose levels, they would be motivated to treat their glucose overproduction if the levels were too high. There is no teaching or suggestion in any cited reference that supports this statement. Furthermore, even if there were, this is irrelevant to the instant claims. Glucose overproduction is not a measure of cell activation, nor is treatment to reduce high glucose a method for reducing cell activation. The instant methods require the step of assessing cell activation, and it if is high, then, administering activation lowering therapy. The cited art does not teach that it is desirable to check levels of cell activation, nor that lowering such levels prior to treatment or for prophylaxis is desirable.

2) The Examiner states that someone who had a trauma would want to know before that condition was treated (if it needed to be treated) by futhan whether or not free radical production had occurred. Again, there is no teaching in any of the cited references nor any art of record that suggests that "someone who had a trauma would want to know [their level of cell activation] before initiating treatment. Again, there is no teaching or suggestion in the cited art for treatment of elevated levels of cell activation, nor for the use of futhan or anything compound or regimen therefor. There is nothing of record to support this conclusion; this is based on teachings in the instant application.

The Examiner is reminded that MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well-known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . ..

MPEP 2144.03 continues:

> If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. In re Malcolm, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

In this instance, a reference or references supporting assertions by the Examiner should be provided. No references of record teach or suggest that such tests are ever performed, that treatment options are evaluated based upon the level of cell activation nor that futhan or any compound or regimen should be used prior to therapy for a disease or condition or as a way to evaluate treatment option nor as a prophylactic.

3) It is alleged that the ordinarily skilled artisan would have been motivated to use a compound like futhan after the detection of elevated free radical production by phenol red assay, to treat the patient in an effort to reduce the free radical production. Again there are no teachings or suggestions in any of the cited references in which measurement of elevated free radical production is performed prior to administering therapy for a particular disease or condition, nor as a prophylactic measure nor to reduce the risk of a poor outcome to a treatment, nor is there any suggestion for using futhan for this purpose..

4) The Examiner concludes that it would have been within the purview of the "skilled artisan" to administer the phenol red assay first to detect the free radical production and, if elevated, the measurement would indicate that treatment for the trauma would need to be performed. Such treatment would be the administration of futhan.

First it is noted that the standard for obviousness, is the level of skill of the ordinarily skilled artisan, not the skilled artisan. Second, it is not revelant whether something is within the level of skill of the ordinarily skilled artisan, if the cited references do not teach or suggest the act that is within the level of skill.

Finally, administration of futhan for treatment of trauma, is not what is claimed. The methods involve assessing cell activation levels, and if elevated, administering cell activation therapy **prior** to performing treatment or administering cell activation, and selecting an alternative treatment. The cell activation lowering therapy is **not** the treatment for the disease (*i.e.*, trauma), but to lower cell activation levels which are responsible for diseases and/or poor treatment outcomes, or risks of certain diseases. Futhan, is selected as the cell activation lowering therpy is administered, not to treat the traumatic injury, but to lower the risks of treatment, such as surgery, for the trauma. There is no suggestion in any cited reference to lower levels of cell activation by treatment with futhan or any treatment or regimen; there is no suggestion to assess such levels.

5) The Examiner states that is would be routine to assess treatment by administering a phenol red assay because it is well known that phenol red assays are used to detect free radical production, 2) treat trauma with futhan because pancreatitis is well known to be treated by futhan, and 3) use a compound like futhan after the detection of elevated free radical production in an effort to reduce the free radical production because traumas are treated with futhan and traumas produce free radicals. No support for these allegations is provided. Again, the Examiner is reminded that of MPEP 2144.03, which requires documentation to support such statements. As noted above, the instant claims are not directed to methods of treating pancreatitis, but to methods in which levels are cell activation are assessed, and if elevated, are

reduced by treatment, not for the underlying disease, but to reduce levels of cell activation.

There is no basis provided for the Examiner's assertion that it would be obvious to use a compound like futhan after the detection of elevated free radical production in an effort to reduce the free radical production because traumas are treated with futhan and traumas produce free radicals. The Examiner has provided no reference that teaches or suggests administration of futhan for following measurement of cell activation, nor for the purpose of lowering cell activation.

Even if the ordinarily skilled artisan had been motivated to use futhan to reduce free radical production, this would not result in the claimed methods. As noted, the clamied methods require the step of assessing cell activation levels prior to administering therapy for a disease, and then based upon the assessment, administering therapy to lower cell activation levels, not for treatment of any particular disease.

None of the cited references, singly or in any combination thereof, teaches or suggests a method of improving treatment outcome or the risk of treatment or for prophylaxis by assessing the level of cell activation, determining if the level is high, and then administering cell activation lowering therapy. Thus, the cited references, singly or in any combination thereof, fail to teach or suggest the elements of the claims.

6) The Examiner states that Gibboni *et al.* teaches that phenol red assays are useful for patients to check their cholesterol or glucose levels. This may be correct; there, however, is no suggestion in this or any reference for assessing levels of cell activation. Gibboni *et al.* teaches methods for detecting hydrogen peroxide in sample; Pick *et al.* teaches a method for assessment of hydrogen peroxide produced by cells in culture, and is of no relevance to the instant claims.

Conclusion

The Examiner has failed to set forth a *prima facie* case of obviousness. Not only would there have been no motivation to have combined the teachings of Okada 1, Okada 2, Yanamoto *et al.* or Yonekura *et al.* Babcock *et al.* or Brunck *et al.* with Gibboni *et al.* or Pick *et al.*, The combination of teachings of the references does not result in a method for assessing treatment options or reducing the risk of a treatment outcome or for prophylaxis, by assessing the level of cell activation in a subject, and, if elevated, treating the subject to reduce the levels of cell activation, prior to any further treatment or as a prophylactic measure.

* * *

In view of the above remarks and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: STOUGHTON *et al.*

Serial No.: 09/038,894

Filed: March 11, 1998

For: *METHODS OF DIAGNOSIS AND TRIAGE USING CELL ACTIVATION MEASURES*

Art Unit: 1651

Examiner Meller, M.

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Michael Lough

MARKED UP CLAIMS (37 C.F.R. § 1.121)

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IN THE CLAIMS:

Please amend claims 10 and 32 as follows:

10. (Amended) A method of improving treatment outcome or reducing risk of treatment, comprising:

assessing treatment options for a disease or condition by measuring cell activation levels in a subject; and, if elevated, administering activation lowering therapy prior to commencing further treatment for the disease or condition, thereby improving treatment outcome or reducing risk of treatment.

32. (Amended) A method of prophylaxis, diagnosis and treatment, comprising:

assessing cell activation; and, if elevated,

administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of treatment of a disease or disorder.

enablement